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Safety, Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of ARGX-119 in Patients With Amyotrophic Lateral Sclerosis: A Phase 2a Study in Progress

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BACKGROUND

ALS: A Fatal Neurodegenerative Disorder

- ALS is a degenerative disorder of the neuromuscular system that is characterized by progressive loss of upper and lower motor neurons, resulting in muscle atrophy and weakness[1–3]
- There is a high unmet need to develop novel therapies for patients with ALS as current pharmacological treatments are limited and have only a modest effect on survival[4,5]

MuSK and ARGX-119

- The agrin-LRP4-MuSK signaling pathway is essential for NMJ establishment, maintenance, and function[6]
- ARGX-119, a humanized, agonistic monoclonal antibody that targets MuSK, is being developed as a novel therapy for patients with neuromuscular disease **(Figure 1)**
- ARGX-119 protected NMJs from muscle denervation and motor neuron degeneration in two *in vitro* NMJ coculture models of ALS[7]
- NMJ dysfunction may play a critical role in ALS disease progression; by activating MuSK, ARGX-119 may stabilize and preserve the NMJ, slowing disease progression,[8] which may improve overall QoL for patients with ALS

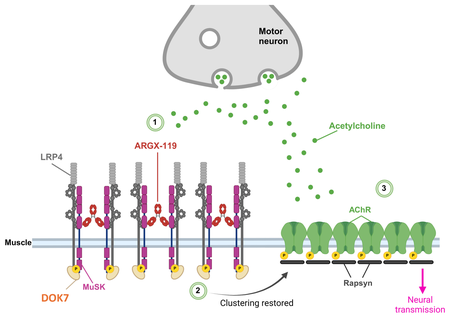
Study of ARGX-119 in Healthy Participants

- Interim results from an ongoing, phase 1 (NCT05670704), FIH, double-blinded, placebo-controlled study of ARGX-119 administered as single doses (IV or SC) or multiple doses (IV) to healthy participants suggested that ARGX-119 had a favorable safety profile at the doses investigated[7,9] **(Figure 2)**

FIGURE 1 ARGX-119 Proposed Mechanism of Action

In ALS, mutations affecting the signaling pathway involved in MuSK dimerization may impact NMJ formation and function.[6] Treatment with ARGX-119 may preserve the NMJ by promoting the dimerization and activation of MuSK

1. Agonistic binding of **ARGX-119** promotes the **dimerization and activation of MuSK,** triggering retrograde signaling to motor axons[8,10,11]
2. Activated **MuSK** phosphorylates downstream **DOK7**, which leads to clustering of **AChR**[8]
3. Acetylcholine binding to **AChR** initiates muscle contraction[8]



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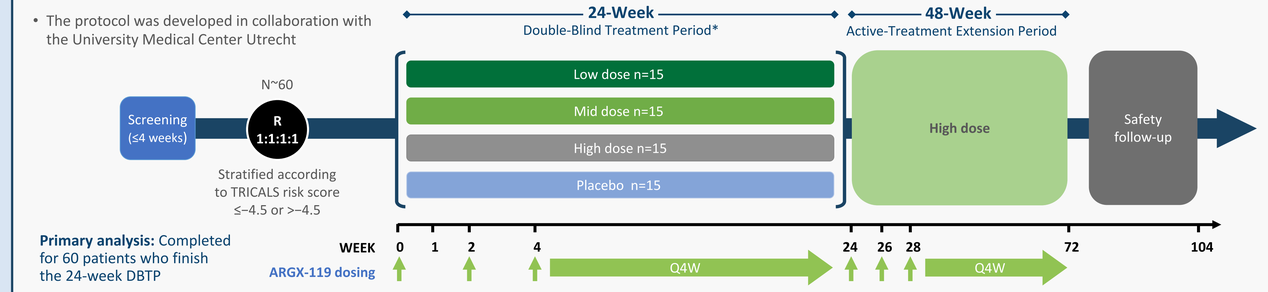
STUDY DESIGN

FIGURE 2 reALiSe Study Design – A Phase 2a, Double-Blinded, Randomized, Placebo-Controlled, and Active-Treatment Extension Study Investigating the Safety and Tolerability, Preliminary Efficacy, PK, and Immunogenicity of ARGX-119 in ~60 Patients With ALS (NCT06441682)



*Blinding to treatment assignment in DBTP will remain throughout the study.

KEY INCLUSION CRITERIA

Diagnosed with familial or sporadic ALS according to Gold Coast criteria[12]

Adults ≥18 and ≤80 years of age

- **TRICALS risk score of ≥–6.0 to <–2.0**
- **SVC of ≥60% of the predicted value**
- **CMAP of >2.0 mV in ≥2 target muscles (APB, ADM, or TA on either side)**

MScan

- The MScan, also known as the CMAP scan, is a new surface-electromyography method from which a MU number estimate can be derived. It has been suggested that this mitigates drawbacks of earlier electrophysiological techniques[13]
- The MScan is non-invasive, easy to apply, highly reproducible, well tolerated, and less labor intensive than various other MU number estimation methods[13]
- It is able to quantify disease progression in muscles affected by ALS and is related to functional decline and survival[13–15]

ENDPOINTS

Primary Endpoint

- Safety and tolerability based on adverse events, clinical laboratory tests, electrocardiograms, and vital signs

Secondary Endpoints

- Rate of change from baseline to Week 24 in MScan-derived MU number
- ARGX-119 PK parameters and the incidence/prevalence of ADA against ARGX-119 in serum over time

Exploratory Endpoints

- Effect of ARGX-119 over time on:
  - Survival at 48 and 72 weeks
  - Electrophysiological markers of disease progression
  - PROs to assess HRQoL and the impact of ALS on activities of daily living
  - Biomarker analysis
  - Mobility
  - Clinical outcomes to assess functioning and loss of autonomy

KEY TAKEAWAYS

ARGX-119 is a humanized, agonistic monoclonal antibody that specifically targets MuSK

Interim results from the ongoing, phase 1, FIH study suggest that ARGX-119 has a favorable safety profile in healthy participants at the doses investigated in single- and multiple-dose cohorts[7,9]

reALiSe is a phase 2a clinical trial investigating the safety and tolerability, preliminary efficacy, PK, and immunogenicity of ARGX-119 in ~60 patients with ALS

A clinical trial application for the reALiSe study has been submitted to the Canadian and EU health authorities. The aim of reALiSe is to assess the potential of ARGX-119 in ALS and support future development

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ABBREVIATIONS

AChR, acetylcholine receptor; ADA, antidrug antibodies; ADM, abductor digiti minimi; ALS, amyotrophic lateral sclerosis; APB, abductor pollicis brevis; CMAP, compound muscle action potential; DBTP, double-blind treatment period; DOK7, docking protein 7; EU, European Union; FIH, first-in-human; HRQoL, health-related QoL; IV, intravenous; LRP4, low-density lipoprotein receptor-related protein 4; MScan, electrophysiological muscle scan; MU, motor unit; MuSK, muscle-specific kinase; mV, millivolt; NMJ, neuromuscular junction; PK, pharmacokinetics; PRO, patient-reported outcome; Q4W, every 4 weeks; QoL, quality of life; R, randomization; SC, subcutaneous; SVC, slow vital capacity; TA, tibialis anterior; TRICALS, Treatment Research Initiative to Cure ALS.

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